

Reagents for Organic Synthesis: Use of Organostannyl Oxides as Catalytic Neutral Agents in the Preparation of Nitriles from Primary Amides under Microwave Irradiation[†]

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The conversion of primary alkyl or aryl amides to their corresponding nitriles constitutes a very useful functional group transformation, and the plethora of reagents for this transformation documented in literature directly demonstrates the importance with which this functional group transformation has been addressed. As early as 1945, this reaction was reviewed,¹ and since then, dehydrating reagents and alternate conditions providing higher yields have been introduced.² Many of these reported methods, however, require the use of highly reactive reagents or harsh conditions in acidic or basic media, or they involve tedious workup procedures. Phosphorus pentoxide³ has been the most common agent for the dehydration of primary amides to nitriles, but many others, including thionyl chloride⁴ or phosphorus oxychloride,⁵ are usually employed.

Recently, alkylating and dehydrating reagents have been introduced that permit the reaction to proceed under mild,⁶ neutral conditions⁷ and at lower temperature⁸ or in liquid triphasic systems.⁹ Unfortunately, the reagents employed so far require special preparation, and the methods are generally limited to only arylamides.¹⁰

Consequently, there is a need for the development of protocols using readily available and safer reagents which lead to high production of nitrile compounds. In view of the current thrust on catalytic processes, there is merit in developing a truly catalytic transformation of amides to nitriles using inexpensive reagents. We report herein a neutral and relatively simple new method for effecting this transformation by using various organotin oxides under microwave irradiation.

In recent years, microwave-induced rate acceleration technology is becoming a powerful tool in organic synthesis¹¹ because of milder reaction conditions, enhanced selectivity, and associated ease of manipulation. Some recent applications include intramolecular Diels–Alder reactions,¹² solid-phase peptide synthesis,¹³ hydrolysis of esters¹⁴ and silyl ethers,¹⁵ *N*-Boc deprotection,¹⁶ etc. Organostannyl oxides have been widely used for the selective manipulation of hydroxyl groups and polyols, particularly in the area of carbohydrates and polyhydroxylated compounds, where preparative procedures typically have to cope with repeated protection/deprotection steps.¹⁷ To the best of our knowledge, however, the generality and applicability of organostannyl oxides in the preparation of nitriles from primary amides under microwave irradiation is not known.

In connection with our current endeavors toward the synthesis of biologically interesting natural products,¹⁸ we explored the opportunity to examine the effect of microwave irradiation on the formation of nitriles. The results of the tin-mediated preparation of nitriles using catalytic amounts of dibutyltin oxide in toluene are illustrated in Table 1. In all the cases examined, the formation of the nitrile is very fast, requiring less than 15 min of overall irradiation time in the microwave oven. The main advantage of our procedure is evident when one compares the reaction time for the formation of nitriles from the primary amides under microwave heating (10–15 min) with that for the standard conditions (overnight in refluxing toluene under standard thermal conditions).¹⁹ In contrast to the previously reported methods, no strong dehydration or expensive reagent is needed, and the reaction can be easily carried out on a large scale under neutral conditions.

The mechanism by which these reactions proceed is particularly intriguing, and we could find no literature precedence for nitrile formation from the amides using

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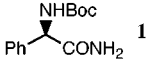
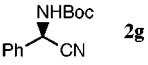
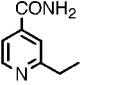
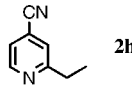
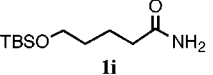
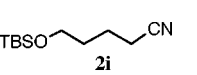
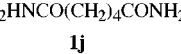
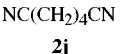
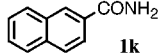
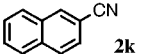
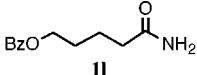
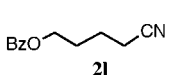
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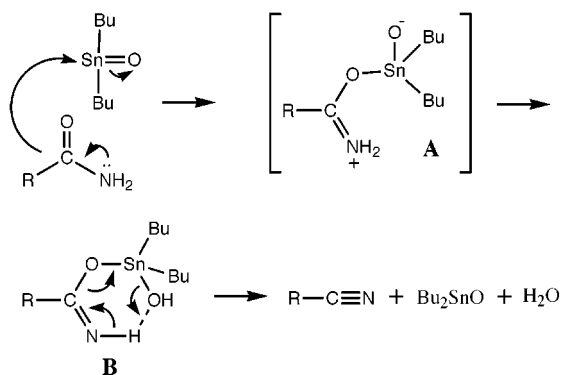
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Table 1. Conversion of Primary Amides to Nitriles with *n*Bu₂SnO and Microwave Irradiation

substrate ^a	product ^b	Yield (%) ^c
C ₆ H ₅ CONH ₂ 1a	C ₆ H ₅ CN 2a	90
C ₆ H ₅ CH ₂ CONH ₂ 1b	C ₆ H ₅ CH ₂ CN 2b	83
2-(NO ₂)C ₆ H ₄ CONH ₂ 1c	2-(NO ₂)C ₆ H ₄ CN 2c	85
3,4-(OCH ₃) ₂ C ₆ H ₃ CONH ₂ 1d	3,4-(OCH ₃) ₂ C ₆ H ₃ CN 2d	88
C ₆ H ₅ CH=CHCONH ₂ 1e	C ₆ H ₅ CH=CHCN 2e	80
Nicotinamide 1f	3-Cyanopyridine 2f	92
 1g	 2g	82
 1h	 2h	95
 1i	 2i	86
 1j	 2j	84
 1k	 2k	93
 1l	 2l	87

^a All substrates were prepared by known literature procedures^b Products were characterized by comparison of their m.p., IR and ¹H NMR spectra with those of authentic samples.^c Unoptimized yields of pure isolated products.**Scheme 1**

organotin oxides. A proposed reaction mechanism is depicted in Scheme 1. On the basis of this mechanism, in principle when the byproduct *n*Bu₂SnO is produced along with nitrile, a catalytic cycle could in turn start. According to this simple idea, it is possible to use a catalytic amount of dibutyltin oxide to perform the desired transformation in high yields. The advantages of the catalytic process are evident: easier workup of the reaction and purification of the product, as well as a more convenient method from the environmental point of view.²⁰ Nitrile formation mediated by dibutyltin oxide can

be envisioned to take place through the intermediacy of structures A and B in Scheme 1. Structure B could actually be favored as a result of the additional ionic interaction by way of hydrogen bonding, although we have no experimental evidence in support of this argument. Thus, when a primary amide is treated with organotin oxide, a reactive stannylated intermediate is formed that subsequently releases the tin reagent, possibly by a template-driven extrusion process, to give the nitrile.

Experimental and theoretical investigations have indicated that the higher the polarity of the organic compound, the more microwave energy it absorbs, which usually causes heating of the material. The different microwave energy absorption of the solvent and/or the reactants and/or intermediates can be advantageously used to alter the course of the reaction carried out in the microwave oven. On the basis of these ideas, we have studied the influences of both the solvent (toluene or xylene) and the organotin oxides [*n*Bu₂SnO or bis (*n*Bu₃-Sn)₂O] on the formation of nitriles from the corresponding primary amides. All the reactions were carried out at 1–5 mmol scale. The results are reproducible. The efficacy of reaction was studied by subjecting substrates **1h** and **1k** in 15 mmol scale under similar conditions. However, it appears that there is no significant improvement in the rate of reaction by changing experimental parameters. It is noteworthy that both acid-sensitive and alkaline-sensitive groups were completely unaffected because of the mild reaction conditions. Neither racemization of the α -bearing carbon²¹ nor β -elimination of the nitrile groups were observed. Furthermore, it appears that electron-donating or -withdrawing groups do not significantly affect the rate of reaction.

In conclusion, the short reaction period, the simple work up, the good yield, and the fairly mild conditions of this method will frequently offer significant advantages over previous procedures, and this approach should be a further interest in synthetic organic chemistry.

General Procedure. Typically, a heterogeneous mixture of the substrates **1a–l** and 0.25–0.35 mol equiv of dibutyltin oxide in dry toluene (10–15 mL per mmol of substrate) was placed in a tube. The tube was then sealed (to prevent evaporation of the solvent) and subjected to microwave irradiation in a commercial microwave oven (operating at 2450 MHz) for 2 min intervals. After this heating, a period of 30 s was allowed for cooling to prevent excess heating. This process was repeated 5–8 times (i.e., total of 10–15 min).²² The cooled tube was opened, and the contents were filtered. The solvent was removed, and the residue was purified by column chromatography (EtOAc/hexane, 1:9 v/v) to afford pure nitriles in 80–95% yields (Table 1). This procedure has been carried out on a 1–5 mmol scale; some experiments have been carried out on larger scales in slightly more concentrated solution and slightly extended overall heating time in the microwave oven.

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(22) During the course of reaction, the temperature inside the microwave oven was also measured, and for the 2 min period, it is around 110 °C. So it is appropriate to use apolar solvent toluene as a medium to carry out the transformations.